

Remarks

Claims 7-12 and 16-34 were pending in the subject application. By this Amendment, claims 17, 18, and 23-26 have been amended, claims 7-12, 16, 19-22, and 27-34 have been cancelled, and new claims 35-39 have been added. The undersigned avers that no new matter is introduced by this amendment. Entry and consideration of the amendments presented herein is respectfully requested. Accordingly, claims 17, 18, 23-26, and 35-39 are currently before the Examiner for consideration. Favorable consideration of the pending claims is respectfully requested.

The applicant and the applicant's representative wish to thank Examiner Marvich for the courtesy of the telephonic interview conducted with the undersigned on October 12, 2005, regarding the rejections under 35 U.S.C. § 112, first paragraph, in the subject application and the continuation-in-part application, U.S. Serial No. 10/759,328. The remarks and amendments set forth herein are consistent with the substance of the interview and are believed to address the outstanding issues as discussed during the interview.

Submitted herewith is a supplemental Information Disclosure Statement (IDS), accompanied by the form PTO/SB/08 and copies of the references listed therein. The applicant respectfully requests that the references listed on the form PTO/SB/08 be considered and made of record in the subject application.

By this Amendment, the applicant has amended claims 17, 18, 23, 24, 25, and 26 and added claims 35-39. Support for the amendment to claim 17 can be found, for example, at page 5, lines 23-32, page 6, lines 1-12, page 7, lines 1-25, page 12, lines 24-31, and page 13, lines 21-28. Claims 18, 23, 24, and 25 have been amended for antecedent basis. Support for the amendment to claim 26 can be found, for example, at page 5, lines 30-32, and page 6, lines 1-6. Support for claims 35-38 can be found, for example, at page 5, lines 30-32, and page 6, lines 1-6. Support for claim 39 can be found, for example, at page 8, lines 12-14, pages 9-10, and page 11, lines 5-7.

Claims 7, 16, 17, 19, 27, 28, 30, and 32 have been provisionally rejected under the judicially created doctrine of "obviousness-type" double patenting as being unpatentable over claims 2-12 and 15 of co-pending Application No. 10/759,328. The applicant respectfully asserts that the claims are not obvious over the cited patent application. However, in order to expedite prosecution of the

subject application, the applicant has submitted a Terminal Disclaimer with this Amendment, which obviates this rejection. Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

Claim 21 has been rejected under 35 U.S.C. §112, first paragraph, as containing new matter. The applicant respectfully submits that claim 21 does not represent new matter. However, claim 21 has been cancelled by this amendment, obviating the rejection. Claim 17 has been amended to recite that the nucleic acid sequence encoding wild-type RhoB protein is introduced into cells associated with the tumor. Support for this amendment can be found, for example, at page 5, lines 23-32, and page 6, lines 1-6, which describe contacting the cancer cell interior with RhoB protein; page 7, lines 1-25, which describes introduction of a nucleic acid construct encoding RhoB into cancer cells; page 12, lines 24-31; and page 13, lines 21-28, which describes transfection of tumor cells lines and implantation in a mouse model.

Claims 7-12, 16-18, and 20-34 have been rejected under 35 U.S.C. §112, first paragraph, as non-enabled by the subject specification. The applicant respectfully submits that the subject specification enables the method of the subject invention. However, as discussed during the telephonic Examiner interview, the applicant has amended claim 17 to recite a method for inhibiting the growth of a tumor in a mammal, comprising administering an effective amount of a nucleic acid sequence encoding wild-type RhoB protein to cells associated with the tumor, wherein the nucleic acid sequence is expressed in the cells. Claims drawn to preventing malignant transformation of a cell (*e.g.*, claim 11) have been cancelled.

The Office Action indicates that the subject specification does not provide sufficient guidance resolving issues associated with *in vivo* delivery of nucleic acids encoding RhoB, particularly for human application. The applicant previously provided Exhibit B with the response submitted to the Patent Office on December 13, 2004, which provides further evidence for the potent tumor suppressive activity of RhoB and confirms the ability to deliver nucleic acids encoding RhoB *in vivo*. The experimental data presented in Exhibit B demonstrates that nucleic acids encoding wild-type RhoB can be delivered within a human lung tumor growing in a mouse model, resulting in inhibited tumor growth. Previously, Dr. Sebti's laboratory showed that forced expression of RhoB in human cancer cells suppresses tumor growth *ex vivo*. As described at pages 16 and 17 of the subject

application, this was done by stably expressing RhoB in human pancreatic cancer cells (Panc-1 cells), subcutaneously injecting these cells into mice, and showing that the RhoB-expressing human cancer cells did not grow. This previous experiment provided evidence for the potent tumor suppressive activity of RhoB. An experiment was then designed to demonstrate that tumor suppression can be achieved by delivering RhoB *in vivo* directly into growing tumors. Under the direction of Dr. Sebti, a nucleic acid sequence encoding wild-type RhoB was cloned into an adenoviral vector. Human lung cancer A-549 cells were injected subcutaneously into the flanks of female athymic nude mice, using the mice as a human tumor xenograft model. When tumors reached an average volume of 150-200 mm³, approximately 5x10¹⁰ adenoviral particles expressing adenoviral-RhoB, adeno-RhoA, or adenovector (vector alone), were injected everyday intra-tumorally for 12 days (150 µl per injection). As is evident from the graph (Exhibit B), A-549 tumors injected intra-tumorally with vector alone grew from 200 mm³ to 800 mm³ over a period of 17 days. In contrast, A-549 tumors injected with adeno-RhoB grew to only 400 mm³. Tumors injected with adeno-RhoA grew to 900 mm³. Thus, in this experiment, it was confirmed that injection of human tumors in nude mice in vivo with adeno-RhoB results in reduced tumor growth. Furthermore, based on the *in vitro* and *in vivo* experimental data provided in the subject application, it is reasonable to expect that the described underlying physiological effects occur *in vivo*, and correlate with suppressed or inhibited tumor growth in mammals. The applicant respectfully submits that one of ordinary skill in the art would accept the *in vitro* and *in vivo* data presented in the subject application and Exhibit B as reasonably predictive of RhoB's therapeutic benefit (*e.g.*, suppression of tumor cell growth) in mammals, including humans.

In regard to animal models, the applicant submits that all that is required by the patent laws is that a "reasonable correlation" exist between the scope of the claims and the scope of enablement. *In re Brana*, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995) and MPEP 2164.02. A rigorous or an invariable exact correlation is not required, as stated in *Cross v. Iizuka*, 224 USPQ 739, 747 (Fed. Cir. 1985):

[B]ased upon the relevant evidence as a whole, there is a reasonable correlation between the disclosed *in vitro* utility and an *in vivo* activity, and therefore a rigorous correlation is not necessary where the disclosure of pharmacological activity is reasonable based upon the probative evidence. (Citations omitted.)

If a particular model is recognized as correlating to a specific condition, then it should be accepted as such unless there is evidence that the model does not correlate. Since the initial burden is on the Examiner to give reasons for lack of enablement, reasons must also be given for a conclusion of lack of correlation for an *in vitro* or *in vivo* animal model example.

The nude mouse tumor xenograft model is an art-recognized animal model of cancer. The human tumor xenograft model utilized in the above-described experiment represents a stringent model for assessment of the therapeutic potential of RhoB. While it is true that there is a continued need to refine and improve pre-clinical cancer models to recapitulate the clinical situation in humans to the extent possible, at the time the subject application was filed, human tumor xenograft models were recognized by those in the field as one of the best tools for conducting pre-clinical *in vivo* analyses of intact human tissue. Submitted with the attached IDS are Kerbel, R.S., *Cancer Biology & Therapy*, July/August 2003, 2:4:Suppl. 1:S134-139; Caponigro, F., *Anti-Cancer Drugs*, 2002, 13:891-897; End, D.W. *et al.*, *Cancer Research*, 2001, 61:131-137; and Shi, B. *et al.*, *Cancer Chemother. Pharmacol.*, 2000, 46:387-393. As stated in the Kerbel publication,

Close inspection of retrospective and prospective studies in the literature, however, reveals that human tumor xenografts—even non metastatic ectopic/subcutaneous ‘primary’ tumor transplants—can be remarkably predictive of cytotoxic chemotherapeutic drugs that have activity in humans, when the drugs are tested in mice using pharmacokinetically clinically equivalent or ‘rational’ drug doses. (Kerbel, abstract; emphasis added)

Disparities between responses observed during pre-clinical studies in the human tumor xenograft model and studies in human cancer patients often attract considerable attention and garner some skepticism. However, when the advanced condition of those patients enrolled in clinical trials is considered in proper context, the clinical predictive value of the pre-clinical human tumor xenograft model must be acknowledged. As stated by the Kerbel publication,

...this skepticism may not always be justified when one takes into account, in retrospect, a crucial and fundamental difference between virtually all published experimental mouse therapy studies and corresponding clinical trials, and it is this: in most phase I, II and III clinical trials the patients being treated have advanced, high-volume metastatic disease whereas most mouse studies do not test the effects of therapy on advanced metastatic disease, but rather on a primary tumor transplant or

spontaneously arising primary tumor, or microscopic, low-volume metastatic disease (Lee Ellis, personal communication). (Kerbel, page S137, emphasis added)

... It is also time to reexamine some of the current dogmas regarding mouse models of cancer. First, human tumor xenografts can be surprisingly predictive of clinical activity, and in some cases this includes subcutaneous/ectopic transplants. The wisdom of the rush towards exclusive use of much more expensive transgenic oncomouse models for drug therapy testing can be questioned, especially when such tumors fail to express the most critical element of malignant disease—ability to metastasize, and the fact that less expensive transplantable tumor models are available which work—if used appropriately. (Kerbel, page S139, emphasis added)

The Caponigro F., End D.W. *et al.*, and Shi B. *et al.* publications demonstrate a correlation between results from pre-clinical human tumor xenograft studies and results from human clinical trials for two different compounds, R115777 and SCH-66336, known as farnesyl transferase inhibitors (FTI). FTI are currently believed to target RhoB (Prendergast and Rane, *Expert Opin. Investig. Drugs*, 2001, 10(12):2105-2116; cited in the Office Action). Also submitted with the attached IDS is the Sun *et al.* publication (*Cancer Research*, 1999, 59:4919-4926), which is co-authored by the inventor of the invention, and demonstrates a correlation of tumor growth inhibition by Taxol® in A-549 cells and lung cancer patients. Advancement of a candidate drug from pre-clinical testing in the laboratory to testing in Phase II clinical trials is based on the assumption that drug activity in cancer models translates into at least some efficacy in human patients, *i.e.*, that cancer pre-clinical laboratory models are clinically predictive. The human tumor xenograft model was art-recognized as an acceptable pre-clinical model for cancer at the time the application was filed, and remains in use today. One of ordinary skill in the art would expect that the experimental results obtained using this model would reasonably correlate with a therapeutic benefit in human patients. Thus, the applicant respectfully submits that the models within the specification and Exhibit B are sufficiently predictive of tumor growth in mammals. As such, the pending claims are commensurate in scope with the experimental findings of the instant disclosure and enabled thereby.

In addition to adenoviral-mediated gene delivery, other techniques for RhoB delivery may be employed, as taught in the subject application. For example, other viral and non-viral vectors may be used to deliver nucleic acid constructs encoding wild-type RhoB to tumor cells, resulting in RhoB expression. Furthermore, tissue-specific promoters may be used, or as taught at page 7, lines 18-23, of the subject specification, event-specific promoters may be used with nucleic acid constructs

encoding RhoB to further optimize and localize expression within the diseased tissues. The Robson *et al.* publication (*J. Biomed and Biotechnol.*, 2003, 2003(2):110-137), which is of record, reviews various methodologies and vectors available for delivering and expressing nucleic acids *in vivo* for the purpose of treating cancer. Among the various targeting techniques available, transcriptional targeting using tissue-specific and event-specific transcriptional control elements is discussed. For example, Table 1 at page 112 of the Robson *et al.* publication lists several tissue-specific promoters useful in cancer therapy, many of which were available at the time the patent application was filed. Tables 2-4 of the Robson *et al.* publication list tumor-specific promoters, tumor environment-specific promoters, and exogenously controlled inducible promoters, many of which were available at the time the patent application was filed. The successful delivery and expression of the p53 tumor suppressor gene *in vivo* has been documented (Horowitz, J. *Curr. Opin. Mol. Ther.*, 1999, 1(4):500-509; Von Gruenigen, V.E. *et al. Int. J. Gynecol. Cancer*, 1999, 9(5):365-372; Fujiwara, T. *et al., Mol. Urol.*, 2000, 4(2):51-54, respectively). As the Examiner is aware, the specification need not disclose what is well-known to those skilled in the art and preferably omits that which is well-known to those skilled and already available to the public. *In re Buchner*, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 231 USPQ 81, 94 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987); and *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 221 USPQ 481, 489 (Fed. Cir. 1984). In view of the means available for delivery and expression of nucleic acids to a human or non-human mammal *in vivo*, and the success demonstrated with these systems, one of ordinary skill in the art would expect that the obstacles to RhoB gene delivery set forth in the Office Action can be addressed by optimization, rather than undue experimentation.

The proper standard for compliance with the enablement requirement is not absolute predictability but objective enablement. Evidence provided by the applicant need not be conclusive but merely convincing to one of skill in the art (see MPEP 2164.05). In other words, a patent specification need not set forth clear and convincing evidence “proving” its conclusions. Rather, the applicant’s statements and assertions are to be taken as true, and rejected only if the underlying facts are found to be untruthful or inaccurate, *i.e.*, only if the asserted claim is “incredible” or “impossible.” *In re Marzocchi*, 169 USPQ 367, 370 (CCPA 1971). The experimental evidence in

the subject specification is sufficiently compelling and fully supports the assertion that delivery of nucleic acids encoding wild-type RhoB reduces tumor growth in mammals. The experimental data provided in the subject application and Exhibit B show that nucleic acids encoding wild-type RhoB can be successfully delivered using methods for gene delivery taught in the subject application and/or known to those skilled in the art at the time the application was filed.

Page 13 of the Office Action indicates that U.S. Patent No. 6,674,980, which the applicant cited in the previous Amendment submitted on December 13, 2004, does not pertain to TAT peptides. The citation of U.S. Patent No. 6,674,980 was a typographical error. U.S. Patent No. 5,674,980 (Frankel *et al.*, "Fusion protein comprising tat-derived transport moiety") was intended.

The applicant respectfully submits that, in view of the disclosure of the subject specification as originally filed, and in view of the experimental results developed using those techniques that are described in the specification and/or known to those of ordinary skill in the art, methods for delivering nucleic acids encoding wild-type RhoB to tumor cells *in vivo* are fully enabled.

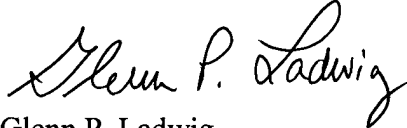
Accordingly, the applicant respectfully submits that, given the teaching of the specification and the state of the art, one of ordinary skill in the art could carry out the claimed method without the need for undue experimentation. In view of the foregoing remarks, reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, first paragraph, is respectfully requested.

In view of the foregoing remarks and amendments to the claims, the applicant believes that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 C.F.R. §§ 1.16 or 1.17 as required by this paper to Deposit Account 19-0065.

The applicant invites the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,



Glenn P. Ladwig

Patent Attorney

Registration No. 46,853

Phone No.: 352-375-8100

Fax No.: 352-372-5800

Address: Saliwanchik, Lloyd & Saliwanchik
A Professional Association
P.O. Box 142950
Gainesville, FL 32614-2950

GPL/mv

Attachments: Petition and Fee for Extension of Time
Supplemental Information Disclosure Statement with form PTO/SB/08 and references
Terminal Disclaimer